Case Reports in Oncology

Case Rep Oncol 2011;4:406–412
DOI: 10.1159/000331263

Published online:
August 24, 2011

ISSN 1662–6575
www.karger.com/cro

Carcinomatous Meningitis: The Natural History of Successfully Treated Metastatic Bladder Cancer

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Key Words

Carcinomatous meningitis · Central nervous system · Complete response · Intrathecal methotrexate · Methotrexate, vinblastine, Adriamycin, and cisplatin combination treatment · Transitional cell carcinoma

Abstract

Carcinomatous meningitis due to bladder cancer is a rare entity reported only in case reports. Optimal therapy is thus poorly defined with earlier cases reporting an unsuccessful outcome. Here we report a case of late carcinomatous meningitis secondary to transitional cell carcinoma (TCC) of the bladder occurring in a patient in complete remission. He was successfully treated with intrathecal methotrexate and whole brain irradiation and experienced prolonged survival after treatment. With modern chemotherapy increasing complete remissions and survival rates in patients with TCC, more and more patients are being reported with carcinomatous meningitis. We raise the question of whether central nervous system prophylaxis should be considered in patients with TCC achieving a complete remission to chemotherapy in the metastatic setting.

Introduction

Carcinomatous meningitis due to bladder cancer is a rare entity reported only in case reports. Optimal therapy is thus poorly defined, with most cases reporting an unsuccessful outcome. Here, we report a case of carcinomatous meningitis secondary to transitional cell carcinoma (TCC) of the bladder successfully treated with intrathecal methotrexate (MTX) and whole brain irradiation.

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Case Report

A 47-year-old white male presented with TCC of the bladder which had metastasized to bone as revealed by PET-CT. Chemotherapy with cisplatin and gemcitabine resulted in a radiographic complete remission after 7 cycles. Three months after completing chemotherapy, the patient presented with headache. A brain MRI suggested carcinomatous meningitis (see **fig. 1**, **fig. 2**). He then developed a right CN III palsy. A lumbar puncture confirmed the diagnosis (see **fig. 3**). The patient was treated with biweekly intrathecal MTX via an Ommaya reservoir for 6 weeks, resulting in the clearance of his cerebrospinal fluid; however, his cranial nerve palsy persisted. He then underwent whole brain irradiation (3,960 cGy at 180 cGy per day over 22 days by the 'German Helmet' technique) with resolution of his cranial nerve palsy. He is currently alive 9 months after his diagnosis of carcinomatous meningitis.

Discussion

Cancer of the urinary bladder is diagnosed in approximately 70,500 people each year in the United States, and about 14,000 individuals die [1]. Central nervous system (CNS) involvement is rarely reported. In a study by Anderson et al. [2] involving CNS complications occurring in bladder cancer, no patient developed carcinomatous meningitis and only 1% of patients developed brain metastasis in a series of 359 patients.

For carcinomatous meningitis associated with other solid tumors, a typical induction regimen consists of a fixed dose of 10 or 12 mg of intrathecal MTX twice weekly for 4 weeks. If clinical response occurs, the frequency of administration is decreased to once weekly for 4–8 weeks; a maintenance regimen is then continued with drug administration every 2 weeks for several months, and then monthly for 2–4 months. The optimal duration of therapy is unknown [3].

The route of delivery of intrathecal chemotherapy may impact outcome. Shapiro et al. [4] demonstrated that MTX administration using an Ommaya reservoir more reliably produced adequate cerebrospinal fluid distribution than administration by lumbar puncture. In another study, 100 patients with clinically and cytologically or radiographically documented neoplastic meningitis stemming from solid tumors received intracerebrospinal fluid liposomal cytarabine or MTX. Progression-free survival (the primary study endpoint) was identical between the sustained-release cytarabine and MTX treatment arms for all 100 patients (35 vs. 37.5 days, respectively, $p = 0.79$). When progression-free survival was examined as a function of the route of chemotherapy administration (lumbar vs. ventricular), there was no difference for patients treated with sustained-release cytarabine (29 vs. 43 days, respectively, $p = 0.35$). For patients treated with MTX, however, there was a statistically significant difference favoring patients receiving intraventricular therapy (19 vs. 43 days, respectively, $p = 0.048$) [5]. Hitchins et al. [6] also noted that responses were more frequent if therapy was administered via an Ommaya reservoir. We speculate that placing an Ommaya reservoir in our patient may have contributed to his relatively prolonged overall survival.

There are several cases of transitional cell carcinomatous meningitis reported in the literature – with our case bringing the total to 30. While some patients presented with grossly widespread disease including the CNS, our literature review suggests that many patients had the complication occur after successful treatment of their systemic disease (see **table 1**). For example, Bishop et al. [7] reported 2 patients developing disease after systemic treatment with MTX, vinblastine, Adriamycin, and cisplatin (MVAC).

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Matsushita et al. [8] reported a case occurring 16 months after their patient had had a complete response following chemotherapy and surgery, and Boukriche et al. [9] reported a case occurring 4 years after adjuvant treatment for resected bladder cancer. Still, just as many cases present concurrently with widespread systemic disease, suggesting that TCC may have an affinity for the CNS and that carcinomatous meningitis may be more common than realized. The prognosis for most patients with carcinomatous meningitis secondary to TCC is dismal, with patients surviving a median of 38 days [31]. Our review confirms the poor prognosis with an average survival of 2.2 months for all patients in which survival has been reported. Interestingly, the average time to the development of carcinomatous meningitis is 14 months (see table 1).

With more cases appearing in the literature, it raises the question: does the successful treatment of systemic disease with modern chemotherapy change the natural history of the disease? Dhote et al. [33] reported on 50 patients with advanced TCC of the bladder treated with MVAC and noted that 8 patients experienced a CNS relapse (16%). In their series, brain metastasis occurred within a mean of 21 months. In the series by Bishop et al. [6], 2 of 17 patients treated with MVAC had carcinomatous meningitis (12%). Finally, in a series reported by Sternberg et al. [34], 2 out of 12 patients achieving complete response on MVAC later developed CNS disease (17%). We can only surmise that in the series by Anderson et al. [2], in which data was collected on patients between 1962 and 2001, the majority of patients did not receive cisplatin-based chemotherapy. With the rising incidence of TCC of the bladder, more and more patients are now dying of complications seen only in advanced stages of disease. With modern chemotherapy, median survival has increased from 3–6 months in the pre-MVAC era to its current figure of almost 1 year. This combination chemotherapy, in a multicenter phase III trial, was shown to increase median survival from 8.2 to 12.5 months [35]. As with any chemotherapy, MVAC is associated with complications like cardiac and renal toxicities, along with neutropenia and mucositis. The rate of death due to MVAC toxicity is around 3–4% and the disease-free survival rate is 3.7% at 6 years [34, 35]. A newer phase III study has shown the clear advantage of using the gemcitabine-cisplatin combination as it is as effective as MVAC, but with less systemic toxicity [36]. Reports of carcinomatous meningitis occurring when the gemcitabine-cisplatin combination is used are increasing, similar to the trend reported for MVAC. As more and more cases appear in the literature, it may be reasonable to consider CNS prophylaxis in patients who achieve complete remission on chemotherapy in a metastatic setting.

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Table 1. Summary of reported cases on transitional cell carcinoma of bladder and its metastasis to CNS

Study first author	Stage at DX	Disease course and treatment summary	CR	Time to CNS disease months	TX CNS	OS after CNS disease months
Hust, 1980 [10]	nr	cobalt XRT	nr	5	none	5
Hust, 1980 [10]	IV	meningitis at presentation	na	0	none	0
Mandell, 1985 [11]	nr	radiation and cystectomy at diagnosis, cisplatin × 5 at relapse	yes	10	IT MTX/XRT	nr
Bishop, 1990 [7]	III	MVAC × 4, meningitis after cycle 4	no	32	IT MTX/XRT	5
Bishop, 1990 [7]	T4	cystectomy, MVAC × 3, meningitis after cycle 3	no	–	none	4
Hussien, 1989 [12]	IV	MVAC × 5, PR, progressed in 3 months, phase I piritrexim with PR	no	9	IT MTX/XRT	5
Raghavan, 1991 [13]	nr	cisplatin and radiation for localized disease relapsed in 16 months, MVAC × 2, IT therapy and MVAC × 4	yes	16	IT MTX-O	4
Eng, 1993 [14]	IV	MVAC × 5, pelvic XRT, PR	no	9	none	0
Eng, 1993 [14]	IV	cisplatin and MTX with CR, relapsed 2 years later	yes	24	IT MTX/XRT	3
Steg, 1993 [15]	nr	nr	nr	nr	none	1
Sugimori, 2005 [16]	IV	presented with meningitis, died of cardiac disease	na	0	none	3
Imamura, 1997 [17]	IV	presented with meningitis	na	0	none	3
Bloch, 1987 [18]	IV	surgery for presumed localized disease, brain metastasis 2 weeks after surgery, whole body XRT, meningitis 3 months later	na	3	–	5
Hasbini, 1997 [19]	T3N2	surgery, MVAC × 4 with CR, meningitis 1 month later	yes	7	–	1
Santarossa, 1997 [20]	T4N3	MVAC × 6, presented 8 months later with meningitis	yes	14	IT MTX/XRT	9
Loizaga, 1998 [21]	I	BCG vaccine, mitomycin B, then developed meningitis	na	15	CMV	0
Cozzarini, 1999 [22]	III	MVAC × 2 with no improvement, surgery, MVAC × 4, then developed meningitis	no	6	IT MTX	3
Cozzarini, 1999 [22]	III	MVAC × 3, PR, surgery, MVAC × 2	no	9	IT MTX	1
Vidal, 2000 [23]	IV	presented with carcinomatous meningitis, 4 doses IT MTX.	na	0	IT MTX	1
Vidal, 2000 [23]	IV	presented with panhypopituitarism, later diagnosed with meningitis	na	1	none	2
Bruna, 2001 [24]	IV	presented with meningitis, died of infection	na	0	IT MTX	2
Bodi, 2004 [25]	I	TURBT	na	9	none	1.5
Matsushita, 2004 [26]	III	MVAC × 3, surgery	yes	16	none	25
Kim, 2005 [27]	nr	surgery	na	108	none	1
Goodman, 2009 [28]	IV	taxol/carboplatin/gemcitabine/trastuzumab, surgery	yes	nr	IT MTX-O	1.5
Butchart, 2010 [29]	II	gemcitabine-cisplatin, XRT	yes	5	none	1
Bowen, 2010 [30]	nr	surgery, gemcitabine-cisplatin × 4	yes	31	XRT	nr
Uncu, 2010 [31]	IV	radiation, gemcitabine-cisplatin × 6, relapsed in lungs in 22 months, gemcitabine-cisplatin resumed, CNS disease 2 months later	yes	36	IT MTX/XRT	2
Zada, 2010 [32]	IV	nr	nr	nr	nr	nr
Tadepalli, 2010 [current report]	IV	MVAC × 7	yes	14	IT MTX/XRT	8

CR = Complete remission; Dx = diagnosis; IT = intrathecal; MTX = methotrexate; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; na = not applicable; nr = not reported; OS = overall survival; PR = partial remission; TURBT = transurethral resection of bladder tumor; Tx = treatment; XRT = radiation.

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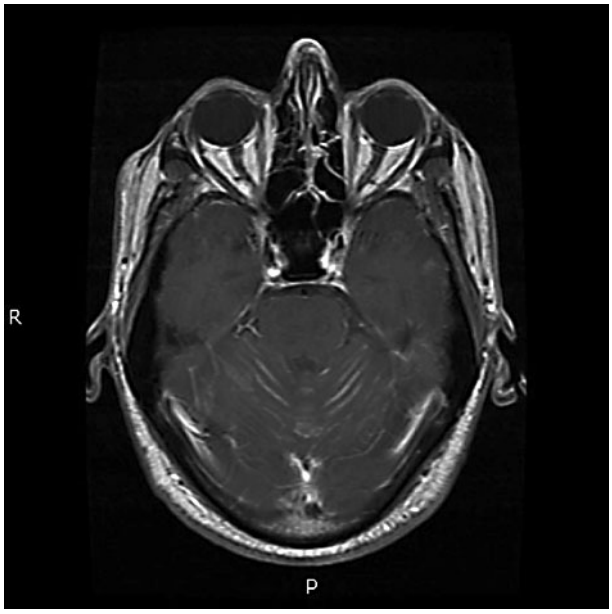

Fig. 1. T_1-weighted gadolinium-enhanced MRI showing abnormal leptomeningeal enhancement patterns of the infratentorial compartment and the supratentorial basal cisterns.

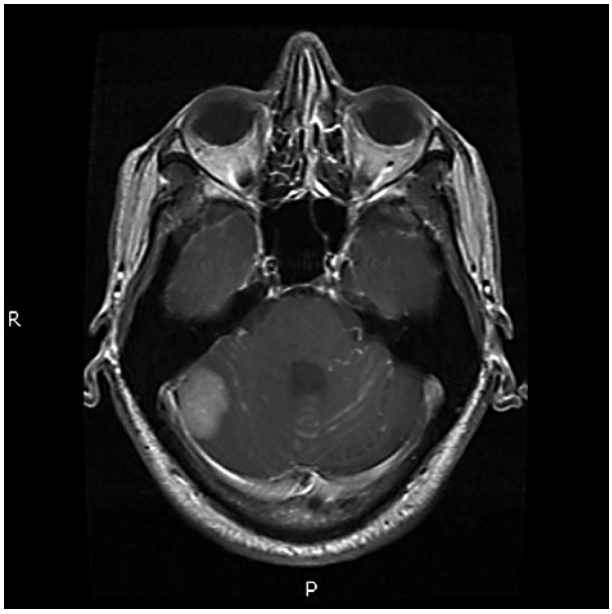

Fig. 2. T_1-weighted gadolinium-enhanced MRI showing left cerebellar encephalomalacia consistent with an old infarct of the left posterior inferior cerebellar artery.

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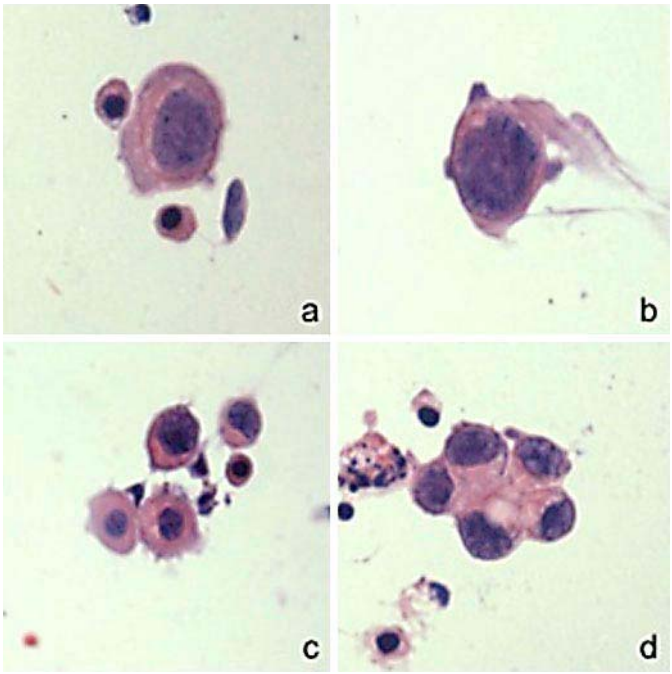

Fig. 3. Cytospin analysis of cerebrospinal fluid reveals numerous malignant cells with features consistent with metastatic high-grade TCC including large, atypical cells with increased nuclear size, prominent nucleoli, and irregular nuclear contours (**a–c**). Clusters of atypical cells with a papillary configuration are also identified (**d**). (HE ×400).

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